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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,401	04/07/2005	Manami Tanaka	081356-0240	6271

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,401	TANAKA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04-07-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 1, 3-5 and 9 are currently pending. Claims 2, 6-8 have been cancelled, and claims 1, 3-5 and 9 have been amended by amendment filed on 06-06-2008.
3. The Examiner acknowledges receiving the following documents: Exhibit A (Ihara et al., 2003, JBC, pp. 24095-24102), Exhibit B, (Kinoshita et al., 1998, American Journal of Pathology, pp. 1551-1560) and Exhibit C (Thomas et al., 1990, Nature pp. 847-850).
4. Therefore, claims 1, 3-5 and 9 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Withdrawn objections/ rejections in response to Applicant arguments or amendment.

Information Disclosure Statement. No copy of References.

In response to Applicant submission of file copies of the references A1, JP-200-13947 and A2, JP 2001-101384 that were not submitted with the IDS documents filed on 04/07/2005 in reply to the Office Action filed on 05-23-2006, and further in view that references A4 and A5 were made of record by the examiner in the PTP-892 form, filed on 12-07-2007, objection to IDS has been withdrawn. Thus information disclosure statement filed on 04/07/2005 has been reviewed, and its references have been considered

as shown by the Examiner's initials next to each citation in the copy attached hereto. References A1, JP-200-13947, and A2, JP 2001-101384, have been considered to the extent that an English abstract is provided.

Objection Drawings

In view of Applicants' resubmission of the originally filed color photographs Figures 3A-D and 4A-D, objection to the drawings for been too dark has been withdrawn.

Remaining objections/rejections in response to Applicant arguments or amendments.

Claim Rejections - 35 USC § 101- Lack of Utility

35 U.S. C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S. C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5 and 9 remain rejected under 35 U.S. C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The instant claim is directed to a chimeric mouse from a mouse embryo wherein the mouse embryo contains a mouse embryonic stem cell introduced therein that has a

genomic DNA containing a disrupted endogenous Bradeion gene, wherein the chimeric rate of said chimeric mouse is from 90% to 98%, and said chimeric mouse exhibits malformation which at least includes one selected from cranial dysplasia, visual disorders, and generalized decreased growth compared with a control mouse of the same strain in which cells containing a disrupted endogenous Bradeion gene has not been introduced. The specification contemplate these mice to "be useful as a model for disorders and/or diseases associated with cerebral neurons and relating to cell canceration" (p. 5, lines 10-15) and for evaluation various treatments in diseases associated with hypoplasia in the cerebral nervous system and malformations (p. 4, lines 10-20). However, none of the asserted utilities of the chimeric mice, comprising a disrupted endogenous Bradeion gene, appears specific and substantial, because they do not correlate to any known function or disease related to the Bradeion gene. The details regarding this rejection are further set forth in the previous office action and in the guidelines above. Applicant's arguments regarding the utility requirement have been fully considered, but not found persuasive.

Response to Applicants' Arguments as they apply to claims 3-5 and 9 under 35 U.S. C. 101.

At pages 5 and 6 of Remarks, Applicants argue that "The claims are directed to a chimeric mouse containing a disrupted endogenous Bradeion gene, with a chimeric rate from 90% to 98%, and exhibits malformation which is at least one selected from the group consisting of cranial dysplasia, visual disorders, and generalized decreased growth compared with those of the same strain without the disrupted Bradeion gene. Thus, the

claimed mouse has a specific genotype (disrupted Bradeion gene), phenotype (cranial dysplasia, visual disorders, and generalized decreased growth) and a high degree of chimerism". In addition, Applicants contend that "The present specification discloses, among others, the usefulness of using the claimed mice in the study of abnormalities in the central nervous system. Page 19, lines 25-29; see also page 4, lines 4-9. Further, the specification discloses that Bradeion is associated with the long-term survival of human cerebral neurons after differentiation (page 4, line 23 through page 5, line 9) and that expression of the human Bradeion gene is found in human adult cerebral nerve system cells, further stating that Bradeion is a potential target for diagnosis and gene therapy for cell mutations (page 2, lines 4-10). Indeed, as briefly noted by the Examiner on page 9 of the Office Action, Tanaka et al. (*Biochem. Biophys. Res. Comm.* (2001) 547-553; Reference A4 of the Information Disclosure Statement filed April 7, 2005) underscores the importance of the Bradeion gene expression in the human central nervous system by showing data indicating its expression in the brain. A person of skill in the art would even expect the correlation of Bradeion gene expression in cancer given its known function as a cell division factor, a process known to be disrupted in cancer. Therefore, while the exact molecular mechanism for the function of Bradeion is not yet known, there is a strong correlation between Bradeion and the central nervous system, as evidenced by gene expression studies in the art as well as the phenotype exhibited by the claimed mice"[emphasis added]. Such is not persuasive.

At page 19, lines 25-29, referred by Applicants, the specification discloses that "In all the chimeric mice, generalized decreased growth, hamster-like faces, relatively large eyeballs, and wandering eyes were observed" and page 4, lines 1-4, recites, "The

present inventors have produced chimeric mice by introducing the embryonic stem cells and clarified that such chimeric mice then exhibit hypoplasia in the overall cerebral nervous system and malformation such as generalized decreased growth, cranial dysplasia, and visual disorders. Thus the present inventors have completed the present invention". In addition, the prior art of Tanaka et al. (*Biochem. Biophys. Res. Comm.* , 2001), also referred by Applicants merely teaches that the Bradeion gene, localized in adult brain, was also found in two human cancers, colorectal cancer and melanoma (Abstract). However, the rejection of the instant claims is not solely based on the absence of a proven chimeric mouse comprising a disruption of the Bradeion gene, including a phenotype characterized by cranial dysplasia, visual disorders, and generalized decreased growth. The prior art is devoid of any teaching for a role or function for the Bradeion, other than its localization to the brain, localization to colorectal and melanoma cancers, and some structural homology to the GTPase motifs conserved in the septin family genes (Tanaka, 2001, Abstract). Therefore, there is no apparent correlation between the function of Bradeion gene and cranial dysplasia, visual disorders, and generalized decreased growth conditions. Thus, in order to determine a specific utility for the chimeric mice, the person skilled in the art would need to perform further research upon the claimed mice in order to determine the correlation between the disruption of the endogenous Bradeion gene in any number of cells and the observed phenotypes and further relating said observed phenotypes to abnormalities of cranial dysplasia, visual disorders, and generalized decreased growth conditions. Thus, in order to determine a specific utility for the mice, the person skilled in the art would need to perform further research upon the claimed mice in order to determine the correlation

between the chimeric mice with a disruption of the endogenous Bradeion gene, the observed phenotypes and their relation to abnormalities of cranial dysplasia, visual disorders, and generalized decreased growth conditions. However, under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not considered substantial utilities. The evidence of record has not provided any other utilities for the chimeric mice encompassed by the claims that are substantial and specific.

At page 7 or Remarks, Applicants allege the usefulness of the claimed mice. To support this position, Applicants cite several publications, including Exhibit A, which according to Applicants "shows the association of a protein of the septin family, of which Bradeion is also a member, with Parkinson's disease", Exhibit B, which "shows the association of septin proteins in Alzheimer's disease" and Exhibit C, recognizing the specifity of the gene knockouts. As such Applicants state, "Without being limited to these findings, it is reasonable, based on the similarity of the Bradeion gene (a septin) with the septins associated with the human neurological disorders as well as the observed phenotype of the mice, to believe that these mice may be useful for the study of these human disorders". Such is not persuasive.

The Examiner does not deny that Bradeion is a novel human septin family gene. However, the association with genes of these family does not recognize a well-established utility and a use with any particular practical purpose as evidence by the disclosure of Exhibit A (Ihara et al., 2003, JBC, pp. 24095-24102), wherein only one

(Sept4) out of five members of the septin protein family (Sept2, Sept5, Sept6, Sept7 and Sept 8) are found to be associated with Neurodegenerative disorders. Likewise, Exhibit B (Kinoshita et al., 1998, American Journal of Pathology, pp. 1551-1560) teaches that at least three of the four septins were localized to the tau-based paired helical filament core. Clearly, the art of record does not evidence a correlation of Bradeion with any of the claimed phenotypes, at the most, it discloses that some of the human septin proteins are localized to the brain inclusions that are hallmark of several neurodegenerative disorders. Hence the utility of the instant invention is neither specific nor substantial for reasons of record. Applicant is reminded that the utility guidelines (see above) expressly state that utilities requiring further research to identify or reasonably confirm a use do not define substantial utilities. Examples of uses that are not considered substantial utilities include basic research in studying the claimed product and use to screen for therapeutics for an unspecified disease. The use of the invention by the skilled artisan does not impart patentability or patentable use on the invention for reasons set forth above. With respect to Applicant's applied reference Exhibit C (Thomas et al., 1990, Nature pp.847-850), the validity of the targeted disruption of the murine int-1 gene regarding the value of the knockout mouse in determining gene function in midbrain and cerebellar development is not questioned. However, the int-1 proto-oncogene is a different gene, more importantantly, the behavioral phenotype of the int-1 proto-oncogene is studied in heterozygous as related to homozygous offspring (p. 849, col. 2). This is not the case in the instant invention. The specification as filed fails to provide specific examples of any cerebral nervous system and malformations disorders modulated by the Bradeion or any evidence that the claimed transgenic mouse would respond differently than that of a wild-

type mouse in any of the claimed phenotypes, in any useful way. In addition, the specification does not teach any phenotypes of less than 90% or more than 98%. Furthermore, as set forth in the previous office action, the instantly claimed phenotypes may result from disruption of other genes in addition disruption of the endogenous Bradeion gene, for example, the art at the time of filing teaches that transgenic mice mutants for specific disruption of the beta-amyloid precursor protein (APP) exhibit cortical dysplasia characterized by focal ectopic neuroblasts (Herms et al., The EMBO Journal, 2004, pp. 4106-4115, Abstract). Conversely, disruption of specific genes may exhibit pleiotropic roles in many different cell types and tissues, for example, expression of Bradeion gene appears to be associated with tumor-specific colorectal cancer and melanoma (Tanaka et al., Biochem Biophys Res Commun. 2001 pp:547-53; p. 552, col. 1). As set forth above and in the previous office action, the phenotypes claimed in the instant invention are not specific or substantial. Applicant is reminded that the requirements under §101 and §112, 1st para. must be met at the time the application is filed. The discovery of a use meeting these requirements after the application is filed does not satisfy the statutory requirements under either §101 or §112, 1st para. See *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967); *In re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 112- First paragraph- Enablement

Claims 1, 3-5 and 9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Applicants' Arguments as they apply to claims 1, 3-5 and 9 under 35 U.S. C. USC § 112- First paragraph- Enablement.

At pages 8-9 of remarks, Applicants argue that the instant claims have been amended to recite the specific phenotype of the chimeric mice including "cranial dysplasia, visual disorders and hypoplasia as compared to the normal mouse, all of which have actually been observed in the chimeric mice, as discussed in the Examples and shown in Figures 3 and 4. Indeed, these characteristics have been observed in multiple chimeric mice generated from at least two different embryonic cell lines, indicating that the scope of the present claims is well supported by the teachings of the specification". Such is not persuasive.

The examiner refers Applicants to the reasons of record and the reasons set forth in the paragraphs above. Hence, one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled. Applicants have not provided guidance to overcome the unpredictability of the nonenabling issues as discussed in the rejection of claims 1, 3-5 and 9 under 35 U.S. C. USC § 112- First paragraph- Enablement- in the previous office action filed on 12-07-2007, including fate of the targeting vector in relation to a particular disruption, the effect of the laboratory environment in the expression of an observed phenotype and the different contributions of the inbred strains of mice commonly used to make chimeric mice.

Conclusion

Claims 1, 3-5 and 9 are not allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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